Hypercapnia invokes an acute loss of contrast sensitivity in untreated glaucoma patients

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Abstract

***Background/aim*—It is widely accepted that hypercapnia results in increased retinal, choroidal, and retrobulbar blood flow. Reports of a visual response to hypercapnia appear mixed, with normal subjects exhibiting reduced temporal contrast sensitivity in some studies, while glaucoma patients demonstrate mid-peripheral visual field improvements in others. This suggests that under hypercapnic conditions a balance exists between the beneficial effects of improved ocular blood flow and some other factor such as induced metabolic stress; the outcome may be influenced by the disease process. The aim of this study was to evaluate the contrast sensitivity response of untreated glaucoma patients and normal subjects during mild hypercapnia.**

***Methods*—10 previously untreated glaucoma patients and 10 control subjects were evaluated for contrast sensitivity and intraocular pressure while breathing room air and then again during mild hypercapnia.**

***Results*—During room air breathing, compared with normal subjects, glaucoma patients had higher IOP ($p = 0.0003$) and lower contrast sensitivity at 3 cycles/degree (cpd) ($p = 0.001$). Mild hypercapnia caused a significant fall in contrast sensitivity at 6, 12, and 18 cpd ($p < 0.05$), only in the glaucoma group.**

***Conclusion*—Glaucoma patients with early disease exhibit central vision deficits as shown by contrast sensitivity testing at 3 cpd. Hypercapnia induces further contrast loss through a range of spatial frequencies (6–18 cpd) which may be predictive of further neuronal damage due to glaucoma.**

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Glaucoma is a disease of the optic nerve resulting in characteristic progressive visual field loss[1] and is believed to be of multifactorial origin.[2] Compromised ocular haemodynamics have been implicated as a major factor in the aetiology of disease.[3–6]

Visual function recovery has been reported following glaucoma therapy. For example, central contrast sensitivity improvement has been demonstrated in primary open angle glaucoma patients (POAG) following IOP reduction via β blocker therapy[7–9] or trabeculectomy,[10 11] and in patients with normal tension glaucoma (NTG) following treatment with a systemic calcium channel blocking agent[12] or topical treatment with dorzolamide.[13]

In addition, it has previously been demonstrated that hypercapnia, when induced by carbogen breathing, results in increased visual field sensitivity in glaucoma patients.[14] The precise mechanism of visual function improvement remains unknown. Increased blood levels of carbon dioxide are known to increase both retinal and choroidal blood flow in animals and humans,[15–17] with several authors having noted a tight link between ocular blood flow and contrast sensitivity in both POAG[18] and NTG patients.[12] It is likely that a population of neurons that is neither fully functioning nor dead, but compromised as a result of the disease, respond positively to the improved circulation.

In animal eyes hypercapnia is also known to result in acidosis with resulting changes in metabolism and consequent compromise in visual function.[19 20] Sponsel *et al*[21] showed that young normal subjects exhibit decreased temporal contrast sensitivity in response to hypercapnia, a finding that would be at odds with a simple hypothesis supporting improved visual mechanisms resulting from improved blood flow in hypercapnia. Similarly, while hyperoxia is known to reduce ocular blood flow[22–25] central vision improvements have been demonstrated in patients with early diabetic retinopathy.[26] These findings indicate that the extent of vasodilatation and consequent ocular blood flow improvement alone are not sufficient to dictate the visual function outcome during gas perturbations. It would seem that in hypercapnia at least, a complex balance exists between the positive effects of improved circulation and some other negative effect, perhaps because of induced metabolic stress. This balance may shift between central compared with peripheral retina or in the diseased state.

The purpose of this study was to determine the effect of hypercapnia on the central vision, measured by contrast sensitivity, of patients diagnosed with glaucoma. Our hypothesis is that the balance between positive circulatory effects and negative metabolic effects due to hypercapnia shifts in central retina, the latter being more sensitive to metabolic compromise and consequent central vision loss in the diseased state.

Materials and methods

Ten previously untreated glaucoma patients and 10 control subjects were recruited for this study. For contrast sensitivity measures, previous data have shown that the test-retest standard deviation for contrast sensitivity measured

using the CSV-1000 is 0.116 log units.[7] With a power of 80% and an alpha level of 0.05, 10 patients are sufficient to show a 0.15 log unit change in contrast sensitivity resulting from the gas condition. This sample size is similar to those from a number of previous studies involving gas perturbations.[22 26]

The experimental protocol and procedures were approved by the University of Alabama at Birmingham institutional review board and all study participants reviewed and signed informed consent statements before participation in the study (Declaration of Helsinki). All patients had glaucomatous type optic nerve head appearance and mild (n = 8) or moderate (n = 2) visual field defects as defined by the Hodapp, Parrish, and Anderson criteria.[27] No limitation was placed on the minimum level of intraocular pressure (IOP) for study inclusion and as such, five of the glaucoma patients had IOPs below 21 mm Hg and were considered to be normotensive. Only patients and subjects with ETDRS acuity less than 0.2 log units (20/30 acuity) were included, thereby excluding eyes with any significant lens opacity. The control group was selected to be similar to the patient group for age, sex distribution, blood pressure, and heart rate such that EDTRS acuity was less than 0.2 log units. Control subjects had no history of ophthalmic disorders and ophthalmic examination was normal. Systemic hypertension was treated in five of the glaucoma patients (two diuretic, two ACE inhibitor, and one calcium channel blocker) and two of the control subjects (two diuretic). One patient and one subject had non-insulin dependent diabetes, but neither had retinopathy.

Before data collection began, patients underwent manifest refraction to achieve the best corrected visual acuity. Each patient's spectacle lens prescription was placed in a lens holder attached to a hand held occluder. The patients held the occluder during vision testing. Best corrected ETDRS visual acuity and contrast sensitivity were assessed in this manner using the CSV-1000 instrument (VectorVision, Dayton, OH, USA). Contrast sensitivity was determined at four spatial frequencies, 3, 6, 12 and 18 cycles per degree (cpd), using a quasi two alternative forced choice procedure.[7 8 28] Subjects practised each test before baseline measurements were taken. Initial baseline visual function measurements were then taken without the presence of any breathing apparatus.

To assess the room air and hypercapnia conditions, subjects wore a face mask that was connected to a non-rebreathing valve. The inhaled air stream originated in a gas mixing chamber, and the exhaled air stream was vented into the examination room. End tidal oxygen and carbon dioxide were monitored by a rapid response gas analyser (BCI International 9004–003 Capnograph/Oximeter; Waukesha, WI, USA) which sampled from the initial portion of the expired air stream. Owing to the inherent risks associated with carbon dioxide breathing, observers were not masked to the gas condition; however, in order to limit bias, neither the study participants nor the observers were aware of the hypothesis of the study. Testing began during the room air breathing condition after the patients had acclimatised to the face mask and had demonstrated consistent respiratory rate and end tidal carbon dioxide levels for 3 minutes.

To produce hypercapnia, end tidal carbon dioxide was increased by manual addition of gas from a 100% carbon dioxide tank to the gas mixing chamber. Testing began during the hypercapnia condition when the patient reached a steady state level of end tidal carbon dioxide 15% above the room air breathing condition, for 3 minutes.[29 30] To ensure no carryover effect from the gas breathing condition during each test session, subjects were evaluated for the room air condition first, and then were tested for the response to elevated carbon dioxide.[15 29]

Blood pressure was monitored using sphygmomanometry, and heart rate and blood oxygen saturation were monitored using a fingertip pulse oximeter. During gas breathing, contrast sensitivity was measured in both eyes and any potential learning effect or test bias was limited as the responses were randomised between patients for the gas conditions. Intraocular pressure measurements were made using the Tonopen (Tonopen, Mentor Inc, Woburn, MA, USA), in order to avoid any requirement for the use of a slit lamp biomicroscope while patients were wearing the face mask.

STATISTICAL ANALYSIS

One eye from each patient was selected at random for data analysis. Paired Student *t* tests were used to assess changes in measures within each group. Unpaired Student *t* tests were used to compare differences between groups for each condition. Bonferroni's correction was applied when multiple *t* tests were performed using a single data set. Pearson product moment correlation analysis was used to ascertain any significant association between variables. A p value of <0.05 was considered statistically significant.

Results

Glaucoma patients and normal subjects were similar for age, sex distribution, blood pressure, heart rate, and ETDRS acuity at baseline (Table 1). Intraocular pressure was significantly higher in glaucoma patients (21.03 (SD 3.92) mm Hg) compared with normal subjects (15.08 (2.35) mm Hg), (p = 0.0003, Table 1). Contrast sensitivity was significantly lower in glaucoma patients than in normal subjects at 3 cpd, both at baseline (p = 0.001) and in room

Table 1 Baseline characteristics of the normal and glaucoma groups

	Glaucoma	*Normal*
Age	54.8 (9.48)	56.4 (8.15)
Sex	4 F/6 M	3 F/7 M
Mean arterial pressure (mm Hg)	103.1 (5.27)	100.7 (6.09)
Heart rate (beats/min)	80.9 (13.8)	74.7 (7.1)
ETDRS visual acuity (logMAR)	0.06 (0.13)	0.012 (0.10)
IOP (mm Hg)	21.03 (3.92)*	15.08 (2.35)*

*Differences between groups at baseline.

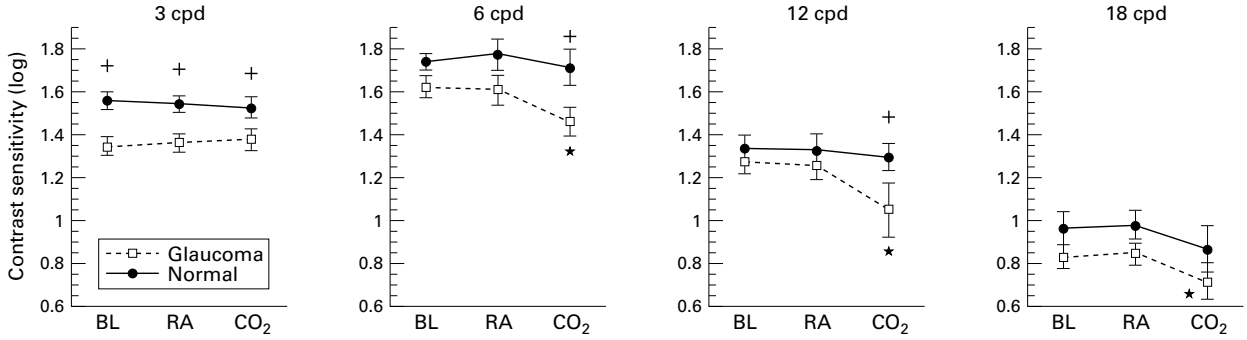

Figure 1 Contrast sensitivity outcomes measured at 3, 6, 12, and 18 cycles per degree (cpd) for glaucoma patients and normal subjects. Measurements were taken at baseline (BL), in room air through a breathing mask (RA), and while breathing carbon dioxide (CO_2). Significant differences between groups are noted by the plus symbol, and differences due to conditions are noted by an asterisk.

air (p = 0.003) conditions (Fig 1). There was no difference between the groups at baseline when tested at 6, 12, or 18 cpd. Neither group displayed any change in visual function when comparing the baseline to room air conditions.

During hypercapnia, end tidal carbon dioxide increased from 37.1 (2.6) to 43.5 (1.3) mm Hg in normal subjects (p<0.0001) and from 36.2 (3.1) to 42.8 (4.1) mm Hg in glaucoma patients (p < 0.0001) (Fig 2). This increase in blood levels of carbon dioxide was associated with an increase in blood oxygen saturation, changing from 95.4% (1.6%) to 96.5% (1.1%) for the normal subjects (p = 0.025) and from 95.8% (0.78%) to 96.8% (0.6%) for the glaucoma patients (p = 0.001) (Fig 3). As shown in Figure 1, hypercapnia caused a significant reduction in the contrast sensitivity of glaucoma patients at 6 (p = 0.015), 12 (p = 0.045) and 18 (p = 0.022) cpd. Also, glaucoma patients displayed significantly lower contrast sensitivity than normal subjects at 3 (p = 0.027), 6 (p = 0.016), and 12 (p = 0.05) cpd during hypercapnia. No changes in blood pressure, heart rate, or IOP were noted for either group when comparing room air with the hypercapnic condition.

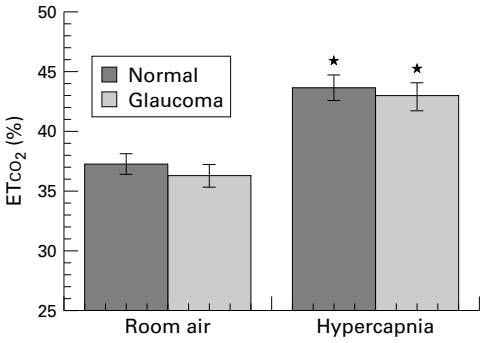

Figure 2 Histogram showing end tidal carbon dioxide levels ($ETCO_2$) in room air and in hypercapnia for normal subjects and glaucoma patients. Significant differences from baseline are indicated by an asterisk.

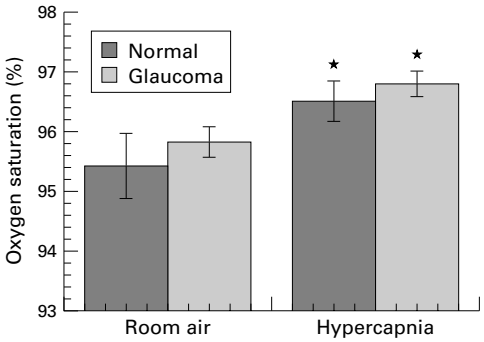

Figure 3 Oxygen saturation levels measured by pulse oximetry in room air and hypercapnia for normal subjects and glaucoma patients. Significant differences from baseline are indicated by an asterisk.

CORRELATION ANALYSIS

No significant correlation was noted between any of the following factors: baseline mean arterial pressure, baseline heart rate, baseline IOP, baseline contrast sensitivity, level of visual field deficit or change in contrast sensitivity with hypercapnia.

Discussion

Our results indicate that during room air breathing conditions, previously untreated glaucoma patients have significantly reduced contrast sensitivity compared with normal subjects at 3 cpd, but not at 6, 12, or 18 cpd. During hypercapnia, glaucoma patients exhibit a further significant reduction in contrast sensitivity, while normal subjects show no change. Our findings are important in two respects. Firstly, the level of hypercapnia achieved was sufficient to differentiate the responses of normal subjects from those of untreated glaucoma patients; secondly, the finding that central visual function reduces in untreated glaucoma patients during hypercapnia.

An important concern in any study of this type is whether the order of testing or the breathing apparatus could influence the contrast sensitivity findings. A small practice effect for contrast sensitivity, which asymptotes by the second testing session, has been previously reported.[21] To potentially offset this effect, all patients conducted a full contrast sensitivity trial on both eyes before baseline measurements were captured. Although the variability of contrast sensitivity testing increases with age,[7] the study groups were matched for age, and the test environment, including room illumination and refractive correction, was carefully controlled. No significant changes were found between the baseline and room air condition for either group. Also, for the normal subjects, no significant changes were noted between any of the test conditions—baseline, room air, or hypercapnia. These data strongly

suggest that the acute vision loss demonstrated by the glaucoma patients was not a result of any systematic bias induced by testing order, the breathing face mask, or some other experimental artefact.

Hypercapnia was achieved by mixing 100% carbon dioxide with intake air in a closed breathing system. It is important in such studies to ensure that the appropriate level of hypercapnia is reached, without replacing too much of the intake air with carbon dioxide, leading to hypoxia. Several aspects of our data suggest that this was accomplished in our study. Firstly, the end tidal measurements show a significant increase in blood levels of carbon dioxide of 43.5 and 42.8 mm Hg for the normal subjects and glaucoma patients, respectively. While clearly facilitating a hypercapnic state, these levels did not appear to be excessive. They were similar to end tidal carbon dioxide levels noted during typical late stage sleep (approximately 41 mm Hg)[31] and were well below those attained during general anaesthesia (approximately 50 mm Hg).[32] Also, blood oxygen saturation increased significantly for both groups. Increased blood oxygen saturation is a well known consequence of mild hypercapnia. The elevated blood levels of carbon dioxide reduce the affinity of haemoglobin for oxygen, causing the release of oxygen into the blood stream (Bohr effect).[33] These results, taken together, indicate that hypercapnia was attained without inducing hypoxia.

Despite broad agreement that hypercapnia induces vasodilatation[15–17] while hyperoxia causes vasoconstriction,[22–25] the visual outcome remains unpredictable. Simplistically, one might anticipate that improved circulation leads to improved visual function, while reduced circulation compromises it. This hypothesis is not supported by Sponsel's finding that young normal subjects exhibit reduced temporal contrast acuity during hypercapnia.[21] It may be that for young healthy tissue at least, other changes such as metabolic stress, possibly from the induced acidosis in hypercapnia, result in compromised neuronal activity, while the beneficial effects of increased blood flow have only a marginal effect on performance. It may be the case that the responsiveness of tissue to the gas state is greater in disease compromised tissue. In diabetic patients, in whom localised tissue hypoxia underlies the disease, induced systemic hyperoxia improves central visual function despite compromised circulation.[26] It would seem that for the diabetics at least, the balance of outcome is shifted in favour of improved visual function due to metabolic improvements rather than a compromised one due to diminished circulation. These findings may be the result of underlying differences in the disease mechanism, or a shift in balance from circulatory to metabolic factors influencing central compared with mid-peripheral vision. In our study, one normal subject and one glaucoma patient was a diagnosed diabetic without ocular involvement. In these cases, the visual response to hypercapnia did not significantly differ from those of the non-diabetic patients and subjects in the study.

Sponsel and colleagues previously demonstrated that young normal subjects decrease temporal contrast sensitivity during hypocapnia and hypercapnia and that the loss during hypercapnia can be blocked by pretreatment with dorzolamide.[21] These results differ from our data in that we found no change in the normal subjects during elevated carbon dioxide. Several differences in the study designs are important to note. In the previous study, subjects breathed 5% carbon dioxide from a premixed tank. They were required to breathe this mixture for 15 minutes after reaching an end tidal level 15% above baseline. In our study, the carbon dioxide levels were tightly controlled using a gas mixing chamber and the end tidal level of 15% above baseline had to be reached for only 3 minutes before testing began. Our design most certainly induced less hypercapnia, possibly providing an insufficient change in physiology to provoke a loss in contrast sensitivity of normal subjects. It is of importance that in our study the normal subjects did show similar trends to the glaucoma patients—that is, falling in contrast sensitivity for 6 and 18 cpd, but these changes did not reach statistical significance. Further, unlike the temporal contrast sensitivity tested at 1 and 4 cpd in the previous experiment, our study evaluated a range of static high spatial frequencies. This difference may be meaningful since the significant changes in contrast sensitivity were noted in our study only for the higher spatial frequencies—that is, 6, 12, and 18 cpd. Irrespective of these differences, it is clear that for the levels of hypercapnia used in our study, untreated glaucoma patients, but not normal subjects, experience a significant fall in contrast sensitivity across a wide range of spatial frequencies.

A further possibility is that the vision loss is caused by a "steal" phenomenon. Studies clearly demonstrate that elevated blood levels of carbon dioxide cause vasodilatation in cerebral and ocular vessels.[15 16 34–37] In glaucoma patients, who may lack ocular vascular autoregulation,[38–41] this generalised vasodilatation could potentially redirect blood flow away from the optic nerve head (ONH) or other critical tissues in the eye. In normal subjects, who possess functional vascular autoregulation, the ONH and other ocular vessels would be capable of sufficient vasodilatation to offset the potential loss of blood flow and contrast sensitivity; this at least is true for the levels of vasodilatation and hypercapnia used in this study.

In summary, glaucoma patients showed a dramatic loss in central vision function, as measured by static high spatial frequency contrast sensitivity, during hypercapnia that was not exhibited by normal subjects under similar conditions. It appears from these data that elevated blood levels of carbon dioxide, either through excessive vasodilatation or some other unknown mechanism, react with the glaucomatous eye to exacerbate the disease related

vision deficit. A potential role for this effect as a diagnostic tool in the evaluation of risk of neuronal damage due to glaucoma, or in determining therapies for glaucoma is yet to be determined.

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